

Fetal origins of coronary heart disease

D J P Barker

The fetal origins hypothesis states that fetal undernutrition in middle to late gestation, which leads to disproportionate fetal growth, programmes later coronary heart disease. Animal studies have shown that undernutrition before birth programmes persisting changes in a range of metabolic, physiological, and structural parameters. Studies in humans have shown that men and women whose birth weights were at the lower end of the normal range, who were thin or short at birth, or who were small in relation to placental size have increased rates of coronary heart disease. We are beginning to understand something of the mechanisms underlying these associations. The programming of blood pressure, insulin responses to glucose, cholesterol metabolism, blood coagulation, and hormonal settings are all areas of active research.

The *BMJ*'s recent editorial on the fetal origins hypothesis stated that it rests only on the "very general" proposition that fetal undernutrition causes coronary heart disease.¹ This is incorrect. The hypothesis states that coronary heart disease is associated with specific patterns of disproportionate fetal growth that result from fetal undernutrition in middle to late gestation.^{2,3}

Disproportionate fetal growth

During embryonic life—that is, during the first eight weeks after conception—the body does not increase greatly in size, but the basic human form is laid down in miniature. The embryo does not contain a description of the person to whom it will give rise,⁴ rather it contains in its genes a generative programme for making a person. In the fetal period, from nine weeks after conception onwards, there begins the phase of rapid growth that continues until after birth. The main feature of fetal growth is cell division. Different tissues of the body grow during periods of rapid cell division, so called "critical" periods.⁵ The timing of these critical periods differs for different tissues. Growth depends on nutrients and oxygen, and the fetus's main adaptation to lack of these is to slow its rate of cell division, especially in those tissues that are undergoing critical periods at the time. Undernutrition slows cell division either as a direct effect or through altered concentrations of growth factors or hormones, of which insulin and growth hormone are particularly important. Disproportionate growth can occur because different tissues have critical periods of growth at different times.

Widdowson and McCance were among the first to show that brief periods of undernutrition may permanently reduce the numbers of cells in particular organs.^{5,6} This is one of the mechanisms by which undernutrition may permanently change or programme the body. Other lasting "memories" of undernutrition include change in the distribution of cell types, in patterns of hormonal secretion, in metabolic activity, and in organ structure. It is not in question that all human beings are programmed.⁷ What is new is an understanding that some of the body's memories of early undernutrition become translated into pathology

—an unsurprising conclusion since numerous experiments in animals have shown that undernutrition for even brief periods in utero leads to persisting changes in blood pressure, cholesterol metabolism, insulin responses to glucose, and in a range of other metabolic, endocrine, and immune parameters.^{3,6}

Size at birth and coronary heart disease

Small size at birth and disproportion in head size, length, and weight are markers of lack of nutrients or oxygen at particular stages of gestation. They reflect adaptations that the fetus made to sustain its development—adaptations that may be permanent. The early epidemiological studies that pointed to the possible importance of programming in coronary heart disease were based on the simple strategy of examining men and women in middle and late life whose body measurements at birth were recorded. The birth records on which these studies were based came to light as a result of the Medical Research Council's systematic search of the archives and records offices of Britain—a search that led to the discovery of three important groups of records, in Hertfordshire, Preston, and Sheffield. The Hertfordshire records were maintained by health visitors and include measurements of growth in infancy as well as birth weight. Preston and Sheffield have detailed obstetric records that document body proportions at birth.

A total of 16 000 men and women who were born in Hertfordshire between 1911 and 1930 have now been traced from birth to the present day. Death rates from coronary heart disease fell progressively between those who weighed less than 5.5 lb (2500 g) at birth and those who were 9.5 lb (4310 g).⁸ A study of men born in Sheffield showed that it was men who were small at birth because they failed to grow, rather than those who were small because they were born prematurely, who were at increased risk of the disease.⁹ In studies exploring the mechanisms underlying these associations it was found that the trends in coronary heart disease with birth weight were paralleled by similar trends in two of its major risk factors, hypertension and non-insulin dependent diabetes. Table 1 shows the size of these trends; the prevalence of non-insulin dependent diabetes and impaired glucose tolerance fell threefold between men who had weighed 5.5 lb at birth and those who had weighed 9.5 lb.¹⁰ This association has been replicated in men and women in three studies

TABLE 1—Prevalence of non-insulin dependent diabetes and impaired glucose tolerance* in men aged 59–70 years

Birth weight (lb (g))	No of men	No (%) with impaired glucose tolerance or diabetes	Odds ratio (95% confidence interval) adjusted for body mass index
≤5.5 (2500)	20	8 (40)	6.6 (1.5 to 28)
5.6–6.5 (2540–2950)	47	16 (34)	4.8 (1.3 to 17)
6.6–7.5 (2990–3410)	104	32 (31)	4.6 (1.4 to 16)
7.6–8.5 (3450–3860)	117	26 (22)	2.6 (0.8 to 8.9)
8.6–9.5 (3900–4310)	54	7 (13)	1.4 (0.3 to 5.6)
>9.5 (4310)	28	4 (14)	1.0
Total	370	93 (25)	χ^2 for trend=15.4 (P<0.001)

*Plasma glucose concentration >7.8 mmol/l at two hours after challenge.

MRC Environmental Epidemiology Unit, University of Southampton, Southampton SO16 6YD
D J P Barker, director

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in Britain, two in the United States, and one in Sweden.³

Adult lifestyle and coronary heart disease

One response to findings such as those in table I has been to attribute them to confounding variables, arguing that people exposed to an adverse environment in utero are exposed to an adverse environment in adult life and that it is this later environment that produces the effects attributed to programming. This suggestion can be examined directly, and the associations between birth measurements and coronary risk factors are found to be unchanged after even the most potent adult determinants of risk are allowed for. For example, the associations between birth size and plasma fibrinogen concentrations are unchanged if smoking is allowed for. Adult lifestyle does, however, add to the effects of intrauterine life. Thus the highest prevalences of impaired glucose tolerance and diabetes, for example, are seen in people who were small at birth and who became obese as adults.¹⁰

There remains the possibility of unknown confounding variables. One way of examining this is to use social class as an indicator of a range of socioeconomic influences, known and unknown. Associations between size at birth and cardiovascular risk factors are found in each social group, whether this is defined at birth or in adult life. Doubt has been cast on the usefulness of data on social class at birth in Hertfordshire because low social class was not associated with low birth weight.¹ There is, however, no evidence that the differences in birth weight found in different social classes in industrial Britain existed in affluent rural counties like Hertfordshire 70 years ago. Furthermore, the usefulness of the information about social class at birth in Hertfordshire is shown by its associations with different infant feeding practices.¹¹

Another way of addressing the issue of unknown confounding variables is to test the associations with size at birth in different populations around the world. Studies in several countries have shown that children who were small at birth have raised blood pressure and evidence of inability to respond to an oral glucose challenge.¹²⁻¹⁴ These findings are further evidence that the associations in adults do not reflect unknown confounding variables linked to lifestyle. Since many of the studies were done in countries where child mortality is low, they also argue against suggestions that associations with birth size reflect bias due to differential survival and selective migration.¹⁵

Insulin resistance

Studies of the Preston records have shown that thinness at birth, measured by a low ponderal index (birth weight/length³), is associated with the "insulin resistance syndrome"—the occurrence of impaired glucose tolerance, raised blood pressure, and disturbed lipid metabolism in adult life.^{16,17} Biochemically the syndrome is characterised by raised serum insulin concentrations, and it leads to coronary heart disease. The Preston study was carried out without prior hypotheses about the specific consequences of thinness at birth. It is therefore helpful that the association with insulin resistance has recently been confirmed in a Swedish study.¹⁸ Furthermore, observations in India that suggest that low birthweight babies have evidence of insulin resistance at the age of 4 years also encourage the view that insulin resistance originates in utero.¹²

The thin neonate lacks skeletal muscle as well as fat, and muscle is the main peripheral site of action of insulin, which has a key role in stimulating cell division in fetal life.¹⁹ It is thought that at some point in middle to late gestation the thin neonate became under-

nourished,² and that in response its muscles became resistant to insulin. Growth of its muscle was therefore sacrificed, but the brain was spared. Studies of the Preston subjects with magnetic resonance spectroscopy have shown that the adults who were thin at birth had reduced rates of glycolysis in their muscles.²⁰ This could indicate persistence of a fetal glucose sparing adaptation. Whether or how it is linked to insulin resistance is unclear. It suggests, however, that detailed clinical studies of adults with known body proportions at birth will be informative. They will be more so if carried out in tandem with studies on animals, in which insulin resistance can be induced by prenatal undernutrition.

Serum cholesterol and blood clotting

Studies of the Sheffield records showed that disordered cholesterol metabolism and blood coagulation in adults were linked to disproportionate size at birth—a short body in relation to the size of the head. This kind of disproportion is thought to result from undernutrition in late gestation: in response the fetus exerts an adaptive response present in mammals and diverts oxygenated blood away from the trunk in order to sustain the brain.²¹ This adaptation prejudices linear growth and growth of the abdominal viscera. The Sheffield records include abdominal circumference at birth as well as body length, and it was specifically reduction in this birth measurement that predicted raised serum low density lipoprotein cholesterol and plasma fibrinogen concentrations in adult life.^{22,23} The differences in concentrations across the range of abdominal circumference were large, statistically equivalent to 30% differences in mortality from coronary heart disease.

Since both cholesterol and fibrinogen metabolism are regulated by the liver one interpretation of these findings is that reduced abdominal circumference at birth reflects impaired liver growth and consequent reprogramming of liver metabolism. Further understanding of liver programming may come more rapidly from studies of animals rather than of humans. Experiments on rats have shown that undernutrition in utero can permanently alter the balance of two liver enzymes, phosphoenolpyruvate carboxykinase and glucokinase, which respectively synthesise and break down glucose.²⁴ A low protein diet during gestation permanently changed the balance of enzyme activity in the offspring in favour of synthesis. It is thought that this reflects enhancement of cell replication in the periportal area at the expense of the perivenous area. These experiments are of particular interest because they showed that undernutrition after birth has no effect, and because the two enzymes are not normally expressed until after birth, which suggests that their expression can be changed before their genes are transcribed.

Studies in Hertfordshire suggest that serum cholesterol concentrations, but not fibrinogen, are programmed by infant feeding. Men who were breast fed for more than one year had raised low density lipoprotein concentrations and increased mortality from coronary heart disease.¹¹ Studies of baboons suggest that these effects could be mediated through thyroxine in breast milk and resetting of the infants' hypothalamic-pituitary-thyroid axis.

Blood pressure

Persisting raised blood pressure seems to be associated with interference with growth at any stage of gestation, since it is found in people who were thin or short babies or proportionately small. Twenty one studies have now shown that low birth weight is

associated with raised blood pressure in childhood and adult life.¹⁴ The relation is not found in adolescence, presumably because the tracking of blood pressure is perturbed by the adolescent growth spurt. In most studies the only birth measurement has been birth weight, which is a crude summary measure of fetal growth. Short babies may have normal birth weight and, as will be described, the ratio of birth weight to placental weight also predicts blood pressure.

Possible mechanisms linking reduced fetal growth and raised blood pressure are persisting changes in vascular structure, including loss of elasticity in vessel walls, and the effects of glucocorticoid hormones.^{25, 26} In animals modest glucocorticoid excess retards intra-uterine growth and programmes raised blood pressure. An excess may occur either from fetoplacental stress or from deficiency in the normal placental enzyme barrier, which protects the fetus from its mother's glucocorticoids. Such a deficiency can be produced experimentally in rats by undernutrition. Fetal undernutrition has also been shown to cause persisting raised blood pressure in rats.²⁷ This must encourage the view that fetal undernutrition is causally linked to hypertension in humans and opens up ways in which the underlying mechanisms can be explored.

Infant growth

Rates of cell division in the fetus fall in late gestation, and growth slows. After birth the nature of growth changes: it depends on the development and enlargement of existing cells rather than addition of new ones.^{5, 6} Failure of infant growth is highly predictive of coronary heart disease in men.⁸ Table II shows that, among the men included in the Hertfordshire records, those who had been small at 1 year of age were three times more likely to die of coronary heart disease than those who had been large. They were also more likely to develop non-fatal coronary heart disease.²⁸ These associations do not depend on the way in which the infants were fed.

There is evidence that infants who fail to put on weight have become resistant to growth hormone, which takes over control of growth from insulin in late fetal life.² Resistance to growth hormone is associated with high circulating concentrations of the hormone, which, it is suggested, may cause cardiac enlargement

and atheroma in blood vessels in the same way that it does in patients with tumours that produce excessive growth hormone. Altered settings of hormonal secretion or tissue sensitivity could prove to be one of the important mechanisms whereby programming leads to pathology.²⁹

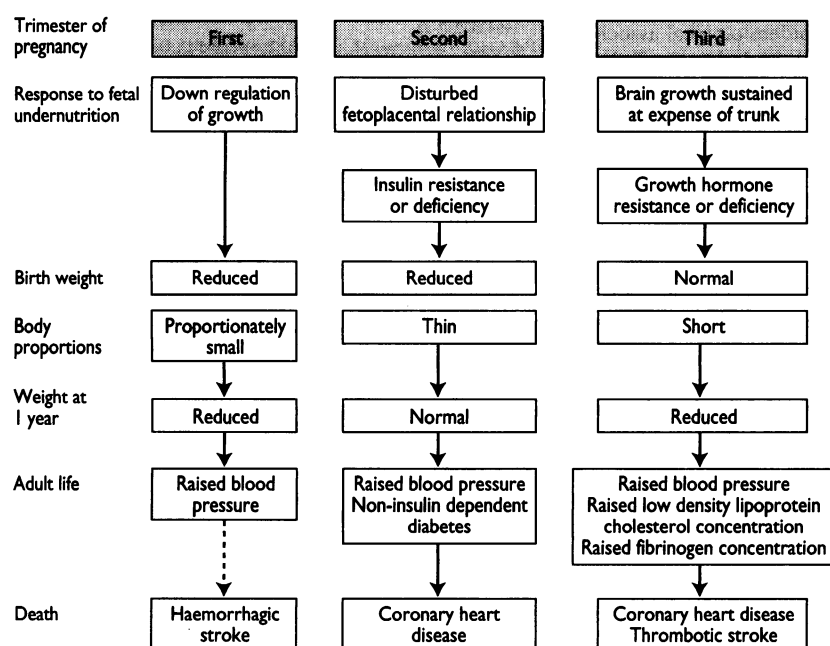
The placenta

Among middle aged men and women in Preston, blood pressure fell with increasing birth weight, as expected.³⁰ At any birth weight, however, systolic pressure rose as placental weight increased. The highest pressures were in people who at birth had large placentas but were relatively small. This was independent of gestation time and was seen when analyses were confined to babies born at term.^{1, 3, 30} Other studies have shown that placental enlargement is also followed by impaired glucose tolerance, disordered blood coagulation, and death from coronary heart disease.³ It is important to note that these untoward effects are linked to heavy placental weight and not merely to a raised placental ratio. Maternal smoking increases the placental ratio because it reduces birth weight more than placental weight, but it does not enlarge the placenta. In any case it seems that maternal smoking is not a major influence in programming the baby¹; it was an uncommon habit among Hertfordshire women in the 1920s, and studies of present day mothers have failed to show that their smoking habits in pregnancy are linked to their children's blood pressures.³¹

In animals, undernutrition in utero may either constrain or stimulate placental growth (reducing or increasing the placental ratio) depending on its nature and timing.^{2, 32} The presence and strength of associations between adult blood pressure and placental weight is therefore likely to vary from one population to another. Undernutrition in early pregnancy in previously well nourished ewes will lead to placental enlargement and is thought to be an adaptation to extract more nutrients. Placental enlargement may similarly be an adaptive response in man.³³ Mothers who are anaemic, who exercise heavily in pregnancy, or who live at high altitude have babies with large placentas. To date studies of maternal nutrition in humans have focused on birth weight and neglected both placental size and body proportions.

TABLE II—Standardised mortality ratios for coronary heart disease in 8175 men by weight at 1 year of age

Weight at 1 year (lb (kg))	Standardised mortality ratio
≤ 16 (7.26)	111
17 (7.71)	140
18 (8.16)	89
19 (8.62)	85
20 (9.07)	87
21 (9.53)	89
22 (9.98)	91
23 (10.43)	68
24 (10.89)	61
25 (11.34)	66
26 (11.79)	51
27 (12.25)	41
≥ 28 (12.70)	36



Framework of ideas in the fetal origins hypothesis linking fetal undernutrition with later abnormalities

Framework of ideas

The studies summarised here led to publication of a framework of ideas within which the links between fetal undernutrition and cardiovascular disease can be explored.^{2, 3} The figure shows this framework, which is a working hypothesis and will need to be re-evaluated as more information becomes available.

Challenges to the hypothesis

DISTRIBUTION WORLDWIDE

Fetal undernutrition and coronary heart disease do not have the same distribution across the world. In China, for example, babies are small at birth, but coronary heart disease is rare.³ We know, however, that in developing countries babies tend to be proportionately small in head size, length, and weight rather than disproportionate as in Western countries.^{3, 34} Animal studies show that undernutrition in early gestation resets the fetal growth trajectory downwards.^{5, 6} This is an important adaptation because it reduces the subsequent demand for nutrients. It leads to a proportionately small baby. Present evidence suggests that this pattern of fetal growth in humans is not associated with coronary heart disease or any of its risk factors other than raised blood pressure. It is

important to establish this point, and a study is in progress in China.

TWINS

Because the fetal growth of twins is retarded it has been suggested that they should have an increased risk of coronary heart disease.^{1,35} Twins are heterogeneous, however, and are a mixture of proportionately and disproportionately small babies.³⁶ A group of twins might have low or high rates of coronary heart disease depending on whether they had predominantly been proportionately or disproportionately small babies. Studies of the long term effects of retarded growth caused by twinning will, however, be of interest aside from this issue.

LARGE BIRTH WEIGHT AND RISK

Several studies have found U shaped associations between birth measurements and coronary risk factors.^{15,37,38} For example, babies with small abdominal circumferences have raised mortality from coronary heart disease, as expected from the associations with cholesterol and fibrinogen, but in babies of above average birth weight a large abdominal circumference predicts raised mortality. Mothers who develop diabetes during pregnancy give birth to macrosomic babies whose abdomen enlarges rapidly in late gestation. Among the Pima Indians there is a similar U shaped relation between birth weight and diabetes, with the large babies being born to mothers with gestational diabetes, which is unusually common.¹⁵ The long term associations of macrosomia need to be examined further.

FACTORS IN CHILDHOOD AND ADOLESCENCE

Although the potential importance of living conditions in childhood and adolescence has been emphasised by some authors, we do not yet know whether socioeconomic influences that affect nutrition and infection in childhood (and thereby influence postnatal growth) can modify the effects of suboptimal growth in utero. Because associations between birth measurements and coronary risk factors are found in childhood it should be possible to carry out short term follow up studies linking measures of fetal growth and growth through childhood to the emergence of risk factors.

The future

We need to progress beyond epidemiological associations to an understanding of the underlying cellular and molecular processes. We need to know what limits the delivery of nutrients and oxygen to the human fetus; how the fetus adapts to limited supply; how these adaptations programme the physiology, metabolism, and structure of the body; and how these programmed changes become translated into pathology. Further research requires a strategy of interdependent clinical, animal, and epidemiological studies. In epidemiology we shall move away from the use of body proportions at birth as markers of fetal nutrition. Ultrasonography provides serial observations of fetal and placental growth, and from studies of children it should be possible to develop better biochemical and physiological markers of fetal under-nutrition. The outline of a strategy for developing the fetal origins hypothesis is now in place; it seems reasonable to expect that it will bring rapid advance.

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